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Cardiovascular morphometry with high-resolution 3D magnetic resonance: First application to left ventricle diastolic dysfunction

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ABSTRACT

In this study, an image-based morphometry toolset quantifying geometric descriptors of the left ventricle, aorta and their coupling is applied to investigate whether morphological information can differentiate between subjects affected by diastolic dysfunction (patient group) and their age-matched controls (control group). The ventriculo-aortic region of 20 total participants (10 per group) were segmented from high-resolution 3D magnetic resonance images, from the left ventricle to the descending aorta. Each geometry was divided into segments in correspondence of anatomical landmarks. The orientation of each segment was estimated by least-squares fitting of the respective centerline segment to a plane. Curvature and torsion of vessels' centerlines were automatically extracted, and aortic arch was characterized in terms of height and width.

Tilt angle between subsequent best-fit planes in the left ventricle and ascending aorta regions, curvature and cross-sectional area in the descending aorta resulted significantly different between patient and control groups (P-values < 0.05). Aortic volume ($P = 0.04$) and aortic arch width ($P = 0.03$) resulted significantly different between the two groups. The observed morphometric differences underlie differences in hemodynamics, by virtue of the influence of geometry on blood flow patterns.

The present exploratory analysis does not determine if aortic geometric changes precede diastolic dysfunction, or vice versa. However, this study (1) underlines differences between healthy and diastolic dysfunction subjects, and (2) provides geometric parameters that might help to determine early aortic geometric alterations and potentially prevent evolution toward advanced diastolic dysfunction.

1. Introduction

Morphometry, i.e., the analysis of a form or shape with quantitative means, has been applied extensively to explore cardiac and vascular anatomy and function. Examples include the detection of anatomical abnormalities [1], preoperative planning and follow-up of patients with cardiovascular diseases [2–4], risk prediction associated with atherosclerosis development [5–8], and cardiovascular devices design support [9]. In particular, morphometry-based analysis finds massive adoption for current research of mapping the effects of natural aging on the structural and functional properties of the aorta [10–17].

Data from those imaging techniques currently adopted in the clinical practice to monitor and assess the cardiovascular function can be leveraged for accurate morphometric analysis. This opens to the possibility of complementing and enriching the information extracted from clinical diagnostic exams. In this regard cardiac magnetic resonance (CMR), bearing the ability to collect precise, quantitative anatomical information, has become a gold standard for heart chambers volumetric analysis and cardiac mass measurements [18,19]. For these reasons, CMR is widely adopted as diagnostic tool for the assessment of the function of the left ventricle (LV), heart failure (HF), and related pathologies, including diastolic dysfunction [20]. Diastolic dysfunction refers to the pathological condition for which the mechanical function of LV during

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diastole is abnormal [21]. The hallmarks of LV diastolic dysfunction are impaired relaxation, loss of restoring forces, reduced diastolic compliance, and elevated LV filling pressure [22].

While systolic function can be routinely assessed non-invasively by measuring markers such as LV longitudinal strain, no consensus currently exists on diastolic dysfunction diagnosis, because no effective image-based clinical indicators of diastolic dysfunction have yet been identified (a detailed overview of the strengths and weaknesses of different imaging modalities for evaluating diastolic dysfunction can be found in Flachskampf et al. [22]). This lack in relevant quantification tools results in a vague understanding of the causes leading to diastolic dysfunction. Moreover, in diastolic dysfunction a set of changes in cardiac mass, orientation and function has the potential to affect the mechanical loading and morphology of the aorta. In parallel, induced alterations in the arterial reflections and in the aortic geometry may result in unfavorable late systolic pressure augmentation, a factor that promotes diastolic dysfunction [22].

In the present study, a morphometry toolset is presented, quantifying geometric descriptors of LV, thoracic aorta and their coupling from 3D CMR images. The proposed toolset is applied to investigate whether the extracted morphological information can be used to differentiate between subjects affected by LV diastolic dysfunction and their age matched controls. The final objective is to investigate if LV diastolic dysfunction is associated with a distortion of the LV-aortic compartment. The proposed image-based morphometric approach could enrich the tools and consequently the information extracted non-invasively, in the direction of understanding the causes and progression of LV diastolic dysfunction [21,22].

2. Methods

2.1. Image acquisition

CMR imaging was performed for a population of diseased and healthy subjects with a prototype self-navigated isotropic 3D balanced steady state free-precession (bSSFP) technique that included a radial readout following a spiral phyllotaxis sampling pattern [23]. The technique was adapted for self-navigation [24–26]. The three-dimensional high-resolution CMR image acquisition was performed with a 1.5 T clinical MRI scanner (MAGNETOM Aera, Siemens Healthcare GmbH, Erlangen, Germany) and the ECG-triggered acquisition was initiated approximately 4 min after injection of a 2 mmol/kg bolus of Gadobutrol (Gadovist, Bayer Schering Pharma, Zurich, Switzerland). Imaging parameters included: TR/TE: 3.1/1.56 ms, FOV: 442 mm^3, matrix: 384^3, acquired voxel size: 1.15 mm^3, radio frequency excitation angle 115°, and receiver bandwidth 900 Hz/Pixel. The trigger delay was set to the most quiescent point of mid-diastole.

2.2. Study subjects

The 3D CMR-based morphometric analysis was applied to a dataset of 20 human subjects. Based on CMR acquisitions, subjects were selected to compose two groups: 10 subjects with diastolic dysfunction formed the patient group (PG), while 10 subjects showing normal LV geometry and both systolic/diastolic functions were selected for the control group (CG). Diastolic dysfunction was considered in the presence of (1) normal LV end-diastolic volume, normal LV ejection fraction (>50%) and increased LV mass (>78 g/m^2 in men; >70 g/m^2 in women), (2) increased LV wall thickness (>12 mm), or (3) LV remodeling (mass to LV diastolic volume ratio > 1 g/ml) [21,22,27–30].

Patient and control groups were matched for age and gender (in total: 6 females, 14 males; age 58.9 ± 12.5 years, range 39–85 years, body surface area (BSA) 2.0 ± 0.26 m^2, range 1.48–2.53 m^2). The ethics review board approved the experimental protocol, and all of the subjects gave informed consent.

2.3. Image segmentation

The cardiovascular regions of interest (ROI) were segmented from the acquired CMR images with a semi-automated expanding region method, that uses a gradient-based edge detection process as implemented in the ITK-SNAP (www.itksnap.org) software [31]. The segmentation process was initiated with a set of manually placed segmentation-defining spheres within the ROI and the corresponding algorithm expands the initial boundaries based on the image data. The cardiovascular structure of the entire aortic trunk including the left ventricle down to the descending thoracic aorta was reconstructed. The descending thoracic aorta was considered to conclude in the level of the renal arteries. The automated segmentation results were visually inspected and any artifacts were corrected with the manual segmentation tool provided by the software. Finally, the segmentation information was exported to stereolithography (STL) file-format for morphometric analysis of the segmented structures.

2.4. Morphometric characterization

The proposed morphometric analysis based the geometric characterization of the anatomical features on the definition of a geometric centerline. In more detail, the centerline **C** is defined and calculated as the locus of the centers of the maximal inscribed spheres along the cardiovascular region of interest. The centerlines are estimated automatically in a form of discrete 3D point sets using the Vascular Modeling Toolkit software (VMTK, www.vmtk.org) [32]. The calculation of local and global features for morphometry characterization is affected by the noise in the estimation of the 3D centerline curves. 3D free-knots regression splines can be employed as a basis of representation to provide a less noisy, analytical formulation of the centerlines [33,34]. A 3D free-knots regression spline of order m is a piecewise polynomial of degree $m-1$, with continuous derivatives of order $m-2$ at the spline knots. The number and the position of the knots are not fixed in advance, but chosen to minimize a penalized sum of squared error criterion [35]. In this study, m was set equal to six, thus allowing the estimation of an analytical formulation for centerlines with no discontinuities in the derivatives of order up to four.

To simplify the comparisons between subjects, we subdivided the aortic trunk in eight regions (R1 to R8) as defined by nine anatomical landmarks (L1 to L9) positioned in: (1) ventricle apex, (2) ventricle base, (3) aortic valve, (4) pulmonary ascending aorta, (5) brachiocephalic trunk, (6) left subclavian artery, (7) pulmonary descending aorta, (8) diaphragm, and (9) renal level (Fig. 1A). In this way, it was possible to break the morphometry analysis in geometric segments. For each centerline segment, a plane fitting the centerline segment was calculated with a least square minimization method, and denoted as best-fit plane in the followings. To characterize the segment orientation, we considered for each plane the normal and tangent vectors, with the latter vector obtained from the linear least-square fit of the projection of the centerline segment onto its respective plane (Fig. 1B). The relative orientation of two subsequent best-fit planes was expressed by a tilt (α) and a twist (θ) angle, calculated as the arccosine of the internal product between the two tangent vectors and the two normal vectors, respectively [36]. Moreover, twist angle can be related to Euler's rotation theorem, stating that a rotation in the 3D space can be expressed as a single rotation around an axis, which is invariant to the rotation. The rotation axis is determined as the line of

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